Review Article

Journal of Scientific Enquiry
Vol: 2(2), Pages: 129-143

Synthesis of Biologically active 2*H*-azirines-A review

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Received: 01.11.2022; Accepted: 06.12.2022; Published Online: 31.12.2022

Abstract

The review contains the biological activity of natural and synthetic 2*H*-azirine derivatives and their synthetic methods to improve their biological activity. 2*H*-azirine derivatives are not only unique synthetic blocks that are indispensable in the synthesis of various classes of organic compounds, but also promising objects for biological research. Recent studies have shown that azirines are stable compounds capable of providing reproducible results in chemical and biological experiments. There is no doubt that the synthesis and biological studies of novel derivatives of azirine carboxylic acids, especially those containing biogenic structural elements or their analogues, will remain the focus of the attention of specialists soon.

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1. Introduction

Nitrogen-containing small ring heterocycles have drawn much attention due to their occurrence in natural compounds and important pharmaceutical potential with a broad range of biological activities.[1] Three-membered azaheterocycles 2*H*-azirines are an important class of heterocyclic family. Due to the high reactivity of 2*H*-azirines enhanced by the ring strain, they can act as nucleophiles, electrophiles, dienophiles, or dipolarophiles in various chemical transformations.[2]Highly strained 2*H*-azirines are weak aromatic heterocycles, which are rare in nature. Very few natural products containing the 2*H*-azirine ring have been described to date.[3] In this review, aware of the increasing interest in chemistry and pharmacology in molecules derived from 2*H*-azirine during the development of new drugs, we have discussed a feasible and convenient synthetic route to the bioactive 2*H*-azirine system.

2. Synthesis of Various type of 2*H*-azirines

2.1 Azirinomycine

Azirinomycine (**1a**) is a naturally occurring antibiotic and is the first example of a natural product, containing an azirine ringwhich was first isolated in 1971. It was isolated from a strain of the soil bacterium *Streptomyces aureus*.[4] It is toxic and therefore cannot not be used in human medicine.

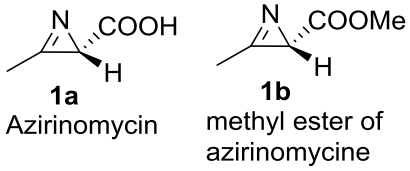
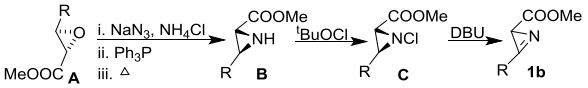


Fig. 1. Azirinomycine and its ester

Azirinomycine (**1a**) was produced by submerged culture in shaken Erlenmeyer flasks in complex organic media. Purification and chemical identification of azirinomycin as 3-methyl-2-(2*H*)azirinecarboxylic acid are reported by Miller *et al*.[5]On the other hand, optically active methyl ester of azirinomycine (2*H*-azirine-2-carboxylic

 DOI:https://doi.org/10.54280/jse.222202

ester, **1b**) was achieved by the Swern Oxidation of the corresponding aziridine-2 carboxylic esters **B** was reported by Zwanenburg and his co-workers in 1995.[6]It was a two-step process involving *N*-chlorination of **B** with tert-butyl hypochlorite and a subsequent dehydrochlorination of **C** with base. The starting materials **B** were conveniently prepared from the corresponding oxirane-2-carboxylic esters **A** by successive treatment with sodium azidein the presence of ammonium chloride and triphenylphosphine and subsequent heating either in acetonitrile or dimethylfonuamide (**Scheme 1**).[7]



Scheme 1. Synthesis of methyl ester of azirinomycine

Azirinomycin and its methyl ester were found to exhibit broad-spectrum antibiotic activity, in vitro, against both Gram-positive and Gram-negative bacteria. Both azirinomycin and its methyl ester are toxic to mice and failed to protect them against lethal bacterial infections.

2.2 Dysidazirine

There are various types of long-chain 2*H*-azirine carboxylates known as Dysidazirine reported in literature.[8]It is strongly levorotatory ($[\alpha]_D$ -165°) and optically active 2*H*-azirines. The first of this family, (S)-(*E*)-dysidazirine (**2a**), was isolated in 1988 from Marine sponge *Dysidea fragilis*, collected in Fiji and shown to exhibit potent antifungal activity against L1210 cells and inhibited the growth of Gram-negative bacteria (Pseudomonas aeruginosa) and yeast (Candida albicans and Saccharomyces cerevisiae) at a minimum concentration of 4 μg per disk in a standard paper disk assay.[9]

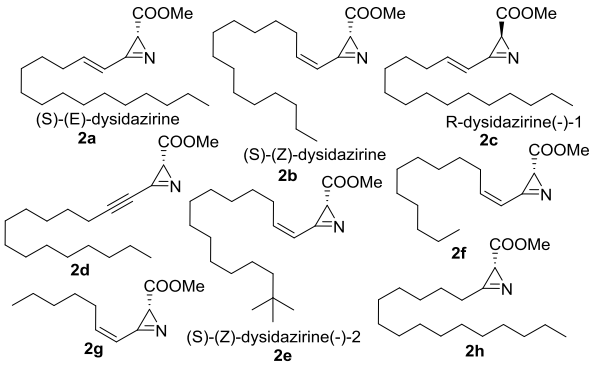
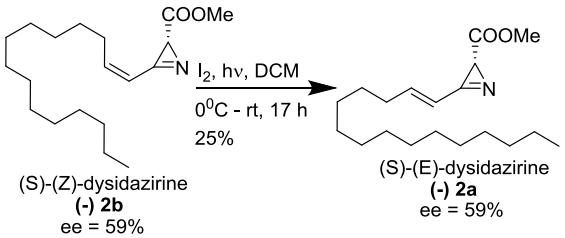


Fig. 2. Various type of Dysidazirine

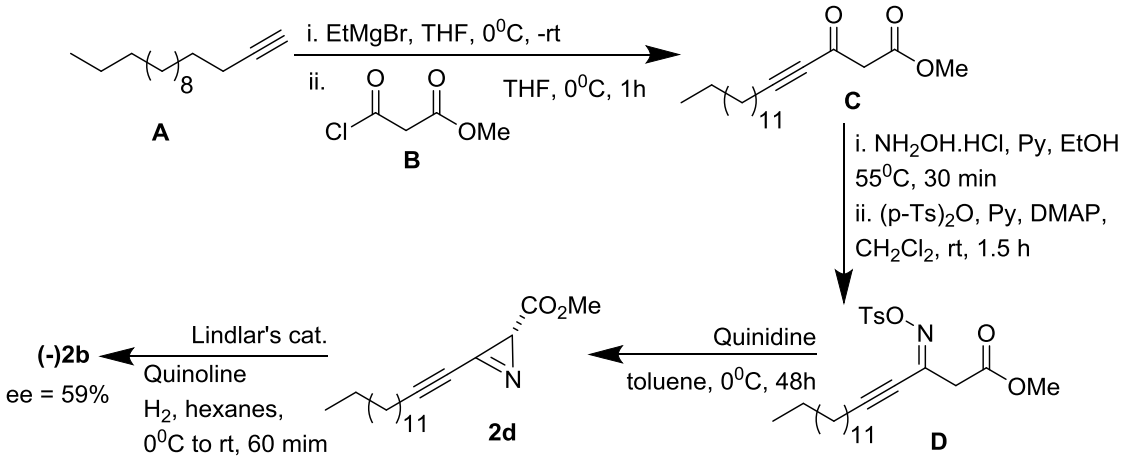
Faulkner and co-workers[10]later reported the isolation of both the (*E*) and (*Z*)geometrical isomers (**2a** and **2b**) of *S*-dysidazirine which are optical isomer of *R*-Dysidazirine (**2c**). A specimen of D. *fragilis* was collected and kept frozen until extraction. However, the optical rotation of this sample was of the opposite sign to that of the literature value, $\{\alpha\}_D$- 165°. So, an authentic sample of dysidazirine**2c** was subsequently obtained from Professor Chris Ireland, University of Utah.



Scheme 2. Photochemical isomerization of (S)-(Z)-dysidazirine to (S)-(E)-dysidazirine

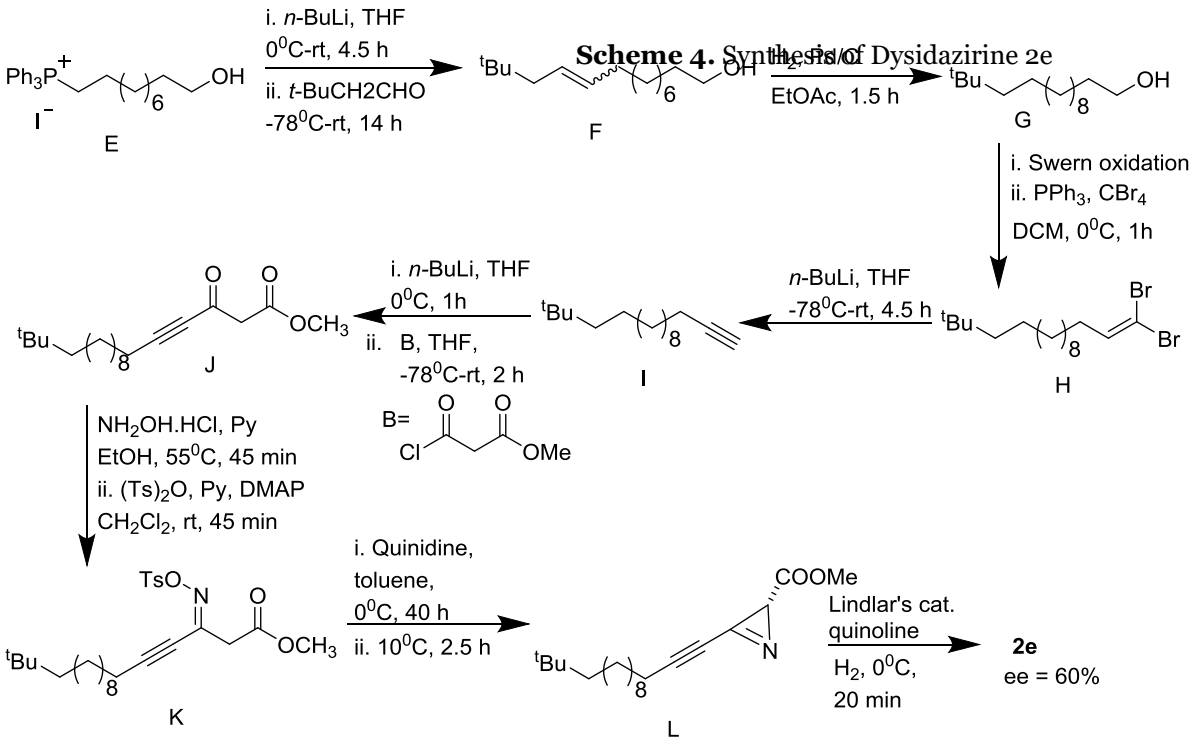
Photochemical isomerization (500W sunlamp, Pyrex) of synthetic (-)**2b** (59% ee) provided (-) **2a** (**Scheme 2**)[8c] in low yield. Natural dysidazirine

and congeneric compounds have all been isolated as non-racemic mixtures of enantiomers. Neat, natural dysidazirine spontaneously epimerizes slowly in the dark and the lack of racemization of **2a** and **2b** in the presence of light excludes a Photochemical mechanism.



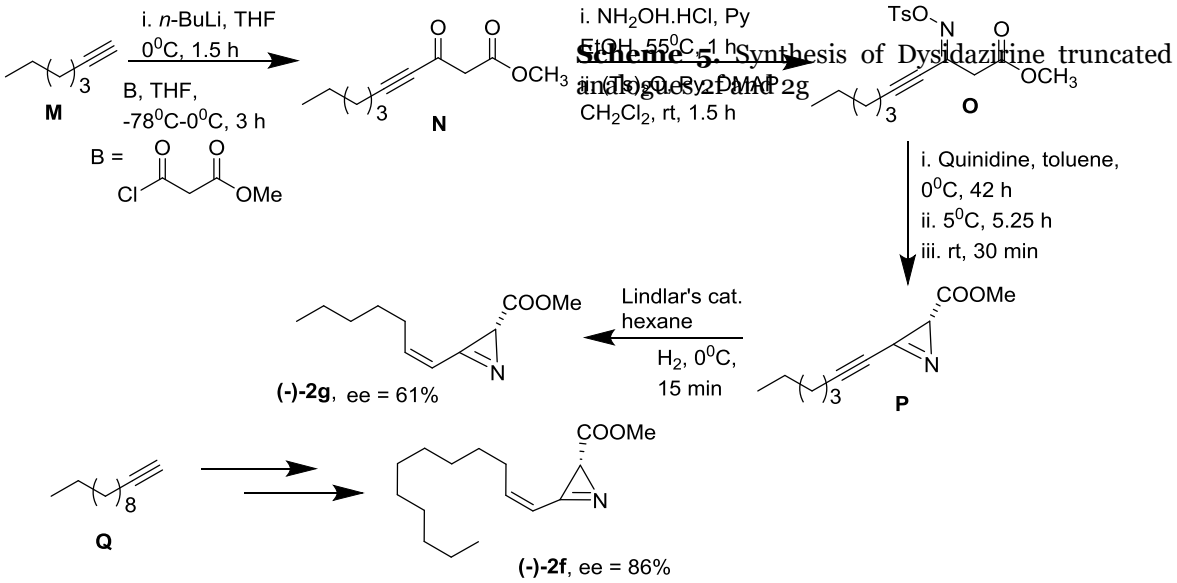
Scheme 3. Synthesis of Dysidazirine 2b and 2d

Synthesis of anotherDysidazirine analogous (**2d-2h**) is also reported.[8]Synthesis of dysidazirine**2d** began with the addition of the lithio-anion of pentadecyne (**A**) to methyl malonyl chloride (**B**). The addition gave poor, variable yields when the deprotonation of **A** was affected with *n*-BuLi; using EtMgBr, however, led to a clean formation of **C** in a reproducible 70% yield. Keto-ester **C** was converted to the corresponding oxime ($NH_2OH{\cdot}HCl$, pyridine, EtOH, 55 °C, 30 min), which was tosylated immediately (*p*-toluenesulfonic anhydride, pyridine, DMAP, 1.5 h) giving **D** in two steps (72% yield). Treatment of **D** with quinidine (0°C, 48 h) lead to clean, albeit slow, formation of the desired 2*H*-azirine ring.[11]While the product azirine was formed with only modest enantioselectivity, this methodology is notable for its practical simplicity and high chemical yield. Partial hydrogenation of (-)-**2d** using Lindlar's catalyst at ambient temperature in EtOH proved difficult due to the facile reduction of the product alkene and the azirine ring within minutes. An improvement was found by lowering the temperature of hydrogenation (0 °C, hexanes) to give (Z)-dysidazirine [(-)-**2b**] in 52% yield and optical purity (59% *ee*) comparable to the related natural products (**Scheme 3**).[8a]



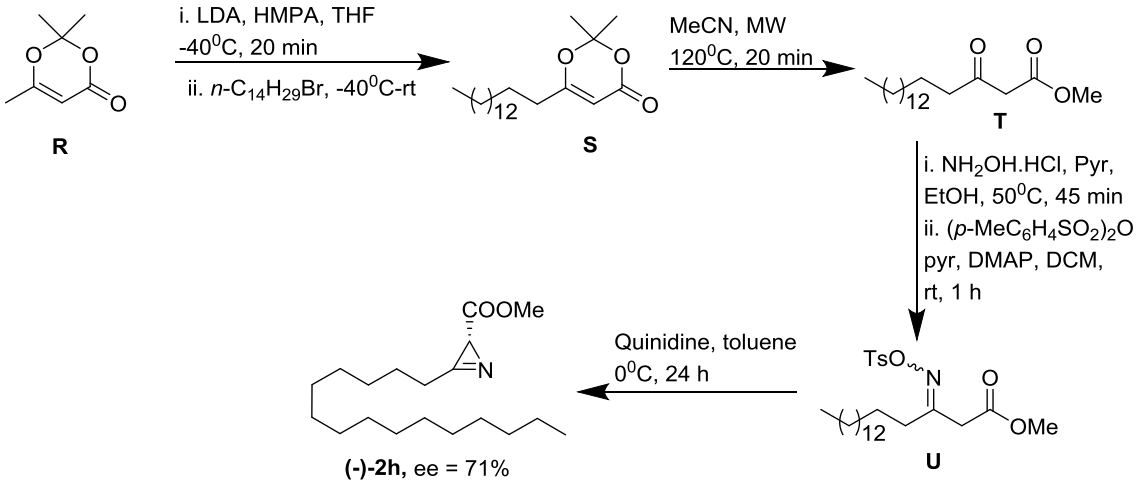
Scheme 4. Synthesis of Dysidazirine 2e

To examine the effect of terminal substitution on antifungal activity, analog (-)-**2e** was synthesized starting with Wittig reaction between phosphonium Iodide **E** and 3,3-dimethylbutanal, giving alkene **F** as a mixture of double bond isomers. Hydrogenation of **F** (H_2, Pd/C, EtOAc, 1.5 h) gave saturated alcohol **G**, which was oxidized under Swern conditions to give the corresponding aldehyde.[12]Treating the crude aldehyde immediately with PPh_3/CBr_4 (DCM, 0°C, 1 h)[12] afforded dibromoalkene**H**, which was subsequently converted to terminal alkyne **I** (*n*-BuLi, THF, -78 °C f rt) in 86% overall yield from **G**. Addition of the lithiated acetylide ion of **I** to **B** proceeded reliably to give **J**, albeit in moderate yield (45%). Keto-ester **J** was converted to the corresponding oximetosylate**K** (71%), which underwent quinidine-mediated cyclization to give the desired azirine (-)-**L** in 80% yield. Cyclization of **K** proceeded even more slowly than the corresponding reaction with **D** and required brief warming to 10°C to ensure complete consumption of starting material. Lindlar reduction of (-)-**L** gave (-)-(*R*)-17,17-dimethyl-(*Z*)-dysidazirine [(-)-**2e**] in 58% yield (**Scheme 4**).



Scheme 5. Synthesis of Dysidazirine truncated analogues 2f and 2g

The addition of the lithio-acetylide derived from alkyne **M** to methyl malonyl chloride gave ketoester**N** in reasonable yield (55%). Treatment of **N** with $NH_2OH.HCl$/pyridine led to the corresponding oxime which was converted to oxime tosylate**O** without purification. Cyclization in the presence of quinidine under Zwanenburg'sconditions[11]provided 2*H*-azirine **P** in excellent yield. Partial hydrogenation with Lindlar's catalyst provided the truncated dysidazirine analog (-)-**2g**. The same sequence applied to alkyne **Q** gave analog (-)-**2f**(**Scheme 5**).



Scheme 6. Synthesis of 4,5-dihydrodysidazirine 2h

Synthesis of (-)-**2h**, the 4,5-dihydro analog of **2b**, began with the generation of the enolate of dioxolane **R** (LDA, HMPA, 40°C) followed by alkylation with 1-bromotetradecane to provide **S** in low yield (18%) along with an equivalent amount of the product from α-alkylation.

Thermolysis of **S** (microwave) gave the incipient ketene that was captured with methanol to afford *O*-methyl β-ketoester**T**, and subsequently converted to oxime tosylate**U** in two steps as before. Treatment of **U** with quinidine led directly to (-)-**2h** in 91% yield(**Scheme 6**).

2.2 Antazirine

Total synthesis of variousantazirines has been achieved from a commercially available starting material, 1,10-decanediol. The key steps involved in this synthesis are Wittig olefination, Corey–Fuchs reaction, Neber reaction, amide coupling.

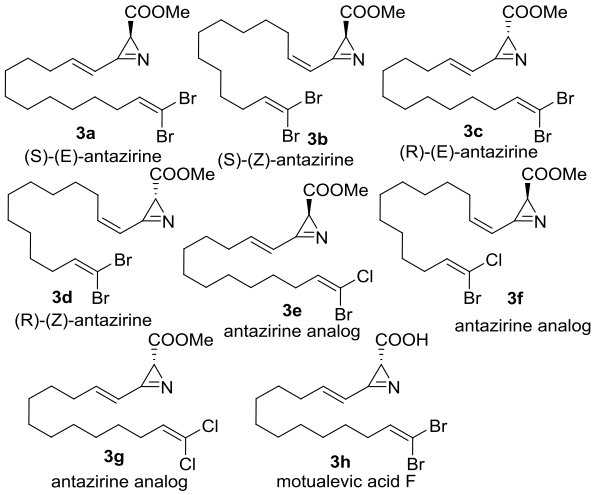
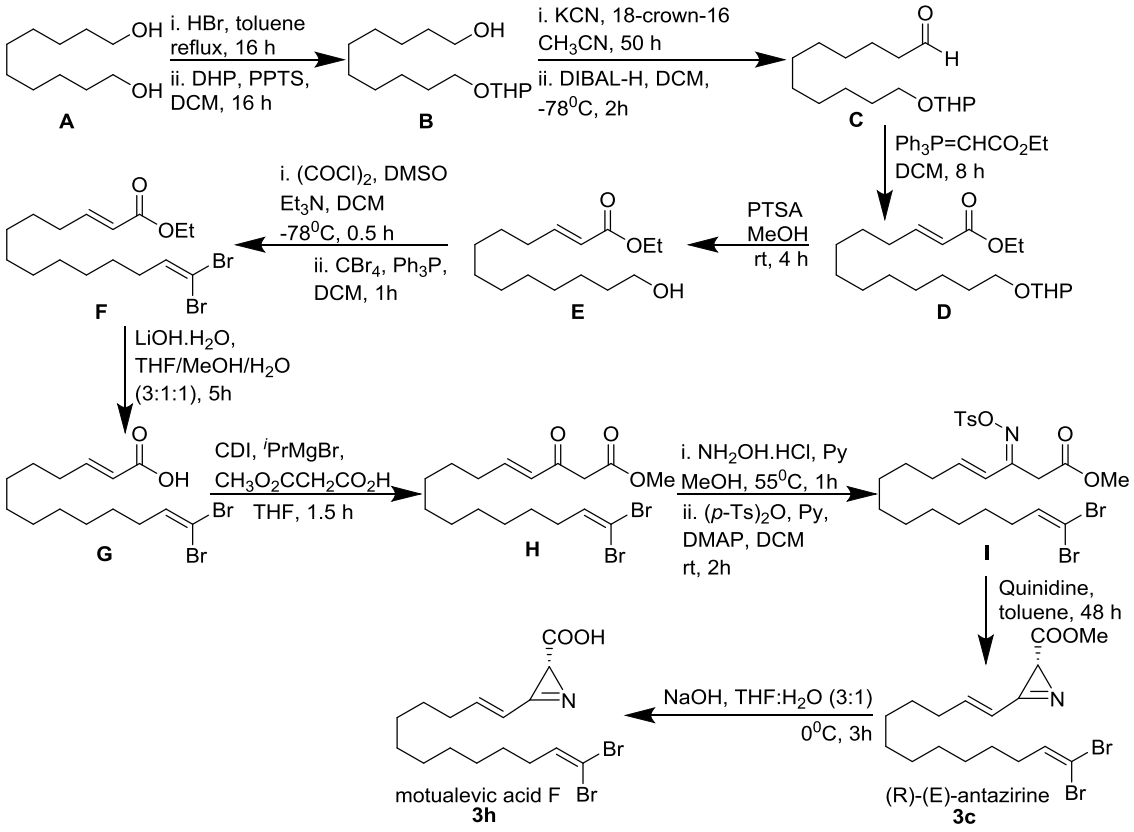


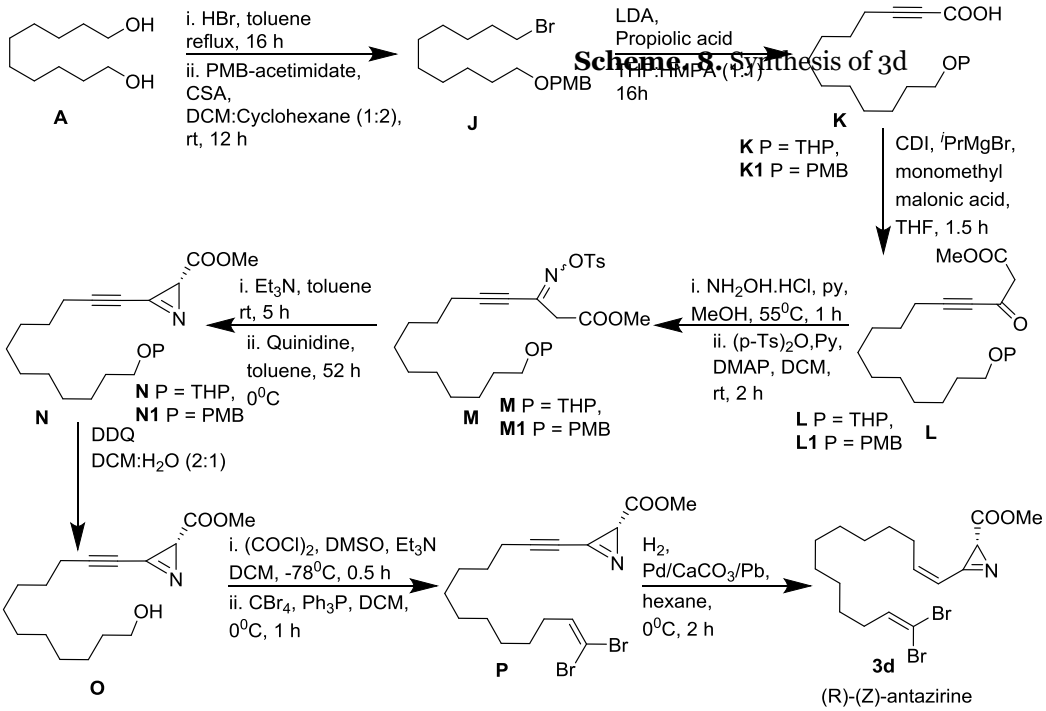
Fig. 3. 2H-azirine containing antazirine analogs



Scheme. 7. Synthesis of 3c and 3h

Further, (*E*)-antazirine (ent-4) and motualevic acid F (**3h**) and (*R*)-(*E*)-antazirine (**3c**) could be accessed from Diol (**A**) as shown in **Scheme 7**. Diol **A** was easily converted to bromofunctionality

intermediate **B**[14] (in 85% yield over 2 steps) by bromination followed by THP ether protection. Treatment of B with KCN in the presence of the catalytic amount of 18-crown-6 in CH_3CN at room temperature gave nitrile,[15]which on reduction with DIBAL-H at -78 °C afforded aldehyde **C**[16] in 75% yield over two steps. Two carbon Wittig olefination of **C** in CH_2Cl_2 at room temperature furnished α, β-unsaturated ester **D** in 80% yield and with complete E selectivity.[17]Deprotection of THP ether moiety in **D** with a catalytic amount of PTSA in MeOH resulted in a primary hydroxyl group **E** in excellent yield. Swern oxidation was performed on **E** to give the corresponding aldehyde, which was subjected to Corey-Fuchs reaction[13]to furnish 1,1-dibromoalkene **F** in 83% yield over two steps. Hydrolysis of ester **F** using LiOH in THF/MeOH/H_2O system resulted the desired motualevic acid E (**G**) in a yield of 72%. Then, motualevic acid E (**G**) was reacted with carbonyldiimidazole (CDI) to give the corresponding imidazolide, which on treatment with the magnesium salt of monomethyl malonic acid[18] afforded β-ketoester[19]**H** in moderate yield. β-Keto-ester **H** was converted to oxime using hydroxylamine hydrochloride in the presence of pyridine in MeOH at 55°C. Subsequently, oxime was treated with Ts_2O, pyridine and catalytic amount of DMAP in CH_2Cl_2 to furnish oxime-tosylate**I** in 40% yield over 2 steps.[8a]To induce the chirality present in (*E*)-antazirine, we have selected a cinchona alkaloid, quinidine, to catalyze the asymmetric Neber reaction.[20] The reaction of tosylated compound **I** with quinidine in toluene at 0°C went smoothly to give the desired (*R*)-(*E*)-antazirine (**3c**) in very good yield and 81% ee. To achieve the synthesis of motualevic acid F (**3h**), hydrolysis of the methyl ester presents in antazirine (**3c**), became the next task. In this direction, optimized base mediated hydrolysis, NaOH, and THF/H_2O (3:1) system at 0 °C was used to accomplish the first total synthesis of motualevic acid F (**3h**) in 85% yield (**Scheme 7**).



Scheme 8. Synthesis of 3d

The synthesis of (*Z*)-antazirine was attempted from the diol (**A**) as shown in **Scheme 8**. diol **A** which was converted to **J** in two steps: bromination followed by PMB protection with *p*-methoxybenzyltrichloroacetimidate, and CSA in a 1:2 mixture of CH_2Cl_2-cyclohexane (85% yield in 2 steps).[21]Reaction of **K** with CDI in THF provided the corresponding imidazolide, which on treatment with the magnesium salt of monomethyl malonic acid in THF gave β-ketoester**L**[19]in moderate yield. Treatment of **L** with hydroxylamine hydrochloride and pyridine in MeOH led to oxime, which was tosylated immediately with TS_2O, pyridine, DMAP in CH_2Cl_2 to give oxime-tosylate**M** in 77% yield (2 steps).[8a] Treatment of **M** with Et_3N in toluene provided azirine **N** in 78% yield. Disappointingly, attempts to deprotect the THP ethereal moiety of **N** using PTSA or CSA in MeOH or CH_2Cl_2were found problematic due to the disturbances in azirine ring. As before, compound **J** was converted to acetylenic acid **K1**,[22]which was reacted with CDI, the magnesium salt of monomethyl malonic acid in THF to give β-keto ester **L1** (57%).[19] The ketoester**L1** was converted to corresponding oxime-tosylate**M1**[8a] (77%, 2 steps), which underwent quinidinemediated cyclization to give the desired **N1** in 77% yield, but only with a low enantiomeric excess (51% *ee*) was observed in alkynyl ketoxime tosylate**M1** comparatively alkenyl ketoxime tosylate**I**. Then, deprotection of PMB group of **N1** with DDQ in CH_2Cl_2/H_2O solvent system provided primary hydroxyl compound **O** in excellent yield without any problem. Oxidation of **O** under Swern oxidation reaction conditions furnished aldehyde, which was immediately and without further purification treated with PPh_3/CBr_4 in CH_2Cl_2 at 0°C to give dibromoalkene**P** in 54% yield over two steps.[13]The acetylenic compound **P** was selectively reduced

with Lindlar catalyst at a lower temperature in hexane under a hydrogen atmosphere to afford exclusively desired (*Z*)-antazirine (ent-5)**3d** in 82% yield (**Scheme 8**).

2.3 Other Bio-active azirines

In addition, in this section we have discussed some other biologically active azirine synthetic method (**4a-4i**).

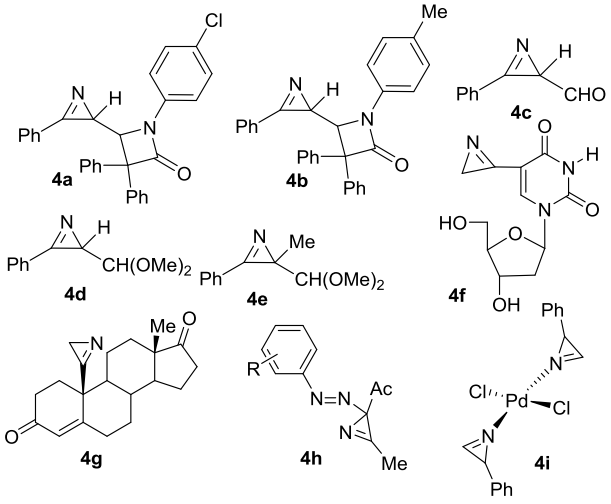
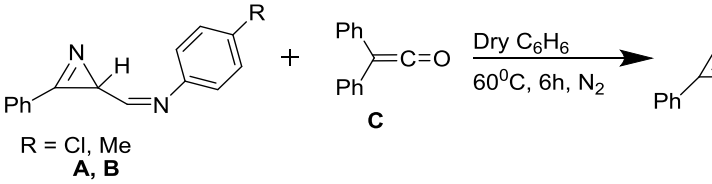


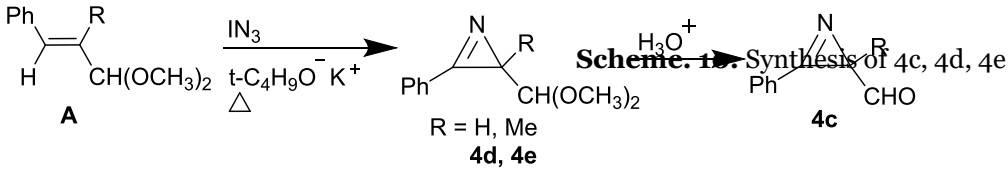
Fig. 4. Some bio-active azirines

Antibacterial and cytotoxic activities of 2*H*-azirines **4a**–**4e**were evaluated. 2-Azetidinones and 2*H*-azirines show antibacterial and cytotoxic activities, however, the biological properties of molecules containing both 2*H*-azirine and 2-azetidinone functions in the same structure are reported. Here, two 2*H*-azirine-2-azetidinones (**4a** and **4b**) and three 2*H*-azirines (**4c**–**4d**) were synthesized from 2-formyl-3-phenyl-2*H*-azirine-*N*-arylimines with diphenylketene. The compounds were assayed for antibacterial and cytotoxic activities. None of them showed antibacterial activity on the tested strains, but both 2*H*-azirine-2-azetidinones showed cytotoxicity against four tumor cell lines (HL-60, leukemia; HCT-8, colon cancer; MDA-MB-435, melanoma; and SF-295, CNS). The IC_{50} values of 1 ranged from 1.1 to 10.5M and from 3.8 to 26.6 μM for**4b**. The mechanism of cell growth inhibition of **4a** and **4b** towards HL-60 cell linewas also investigated. Membrane damage, cell viability, DNA synthesis inhibition, and morphological changeswere evaluated. The preliminary findings suggested that **4a** and **4b** induce apoptosis.[23]



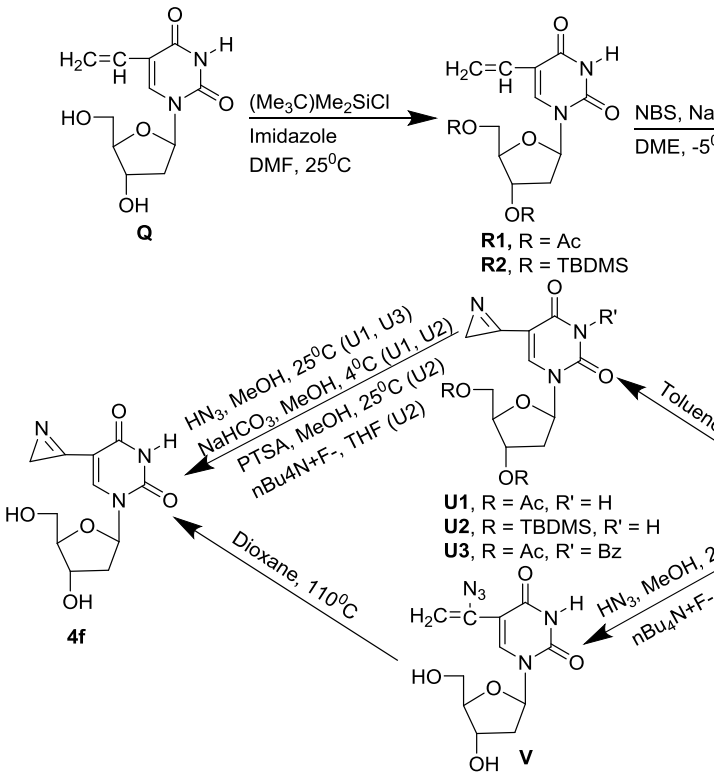
Scheme. 9. Synthesis of 4a and 4b

2-Formyl-3-phenyl-2*H*-azirine-*N*-arylimines (**A, B**) (prepared by reaction of the appropriate aniline and 2-formyl-3-phenyl-2*H*-azirine) reacted smoothly with diphenylketene **C**(generated by thermal decomposition of diphenyldiazoethanone)in benzene (60°C, 6 h, nitrogen atmosphere) to afford 2*H*-2-arzirinyl-2-azetidinones (**4a**&**4b**) (**Scheme 9**).[24]



Scheme. 10. Synthesis of 4c, 4d, 4e

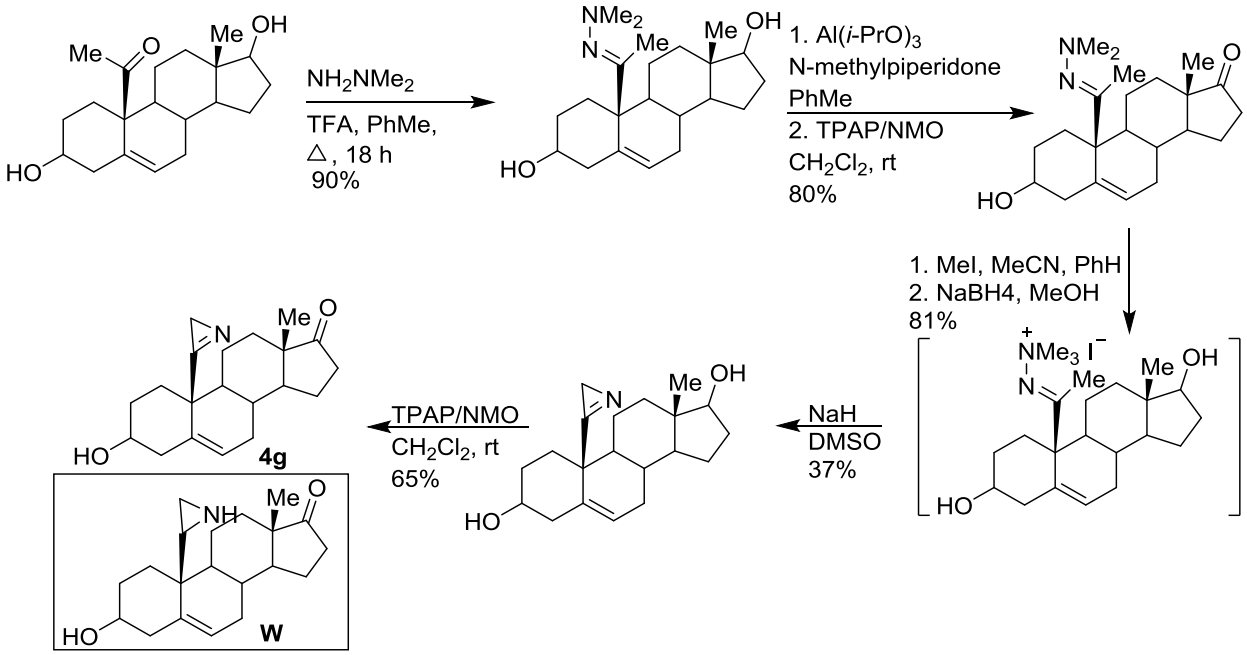
Azirine **4d** and **4e** were readily prepared by the addition of iodine azide to the dimethyl acetal of cinnamaldehyde followed by dehydrohalogenation and thermolysis. After aqueous hydrolysis azirine **4c** was isolsted (**Scheme 10**).[25]



Scheme 11. Synthesis of 4f

The in vitro antiviral activities of 5-[2-(1-azirinyl)]-2'-deoxyuridine (**4f**) was determined against four viruses (herpes simplex virus type 1 (HSV-l), type 2 (HSV-2), cytomegalo virus (CMV), and varizella zoster virus (VZV)). The observation that the 5-[2-(1-azirinyl)] compound **4f** was an inactive antiviral agent was unexpected since the azirinyl ring system is conjugated with the 5,6-olefinic bond and it is an electronegative hydrophobic moiety.Imidazole and tert-butyldimethylsilyl chloride (TBDMSCI) were added to a solution of **Q** in DMF and the reaction was allowed to proceed at 25°C with stirring for 36 h. The regiospecific addition of bromine azide to the 5-vinyl substituent of the 2'-deoxyuridine derivative (**R1** and **R2**) afforded the corresponding 5-(1-azido-2-bromoethy1)-2'-deoxyuridine analog (**S1**, 88%) and (**S2**, 82%), respectively. To prevent the formation of the bicyclic product, the N-3 position of 5-(1-azido-2-

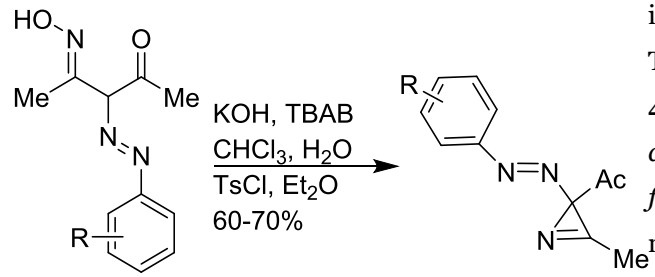
bromoethyl)-3',5'-di-O-acetyl-2'-deoxyuridine (**S1**) was protected by the reaction of **S1** with benzoyl chloride in dry pyridine, which gave the N-3 benzoyl derivative (**S3**) in 93% yield. The reaction of **S3** with ^{t}BuOK in THF yielded the 5-(1-azidovinyl) analog **T3** in a higher yield (39%) than that obtained using **S3** (27%). The reaction of the 3',5'-di-O-acetyl derivative **S3** with ^{t}BuOK in THF gave rise to three products (**T1, T2, T3**). Deprotection of **T1** (NH_3-MeOH) and **T2** ($^{n}Bu_4N^{+}F^{-}$-THF) yielded 5-(1-azidoviny1)-2'-deoxyuridine (**V**) in 76 and 86% yield respectively. 5-(1-azidovinyl) compounds **T1-T3** in dry toluene at 110°C afforded the corresponding 5-[2-(1-azirinyl)] analogs **U1-U3** in 24, 84, and 54% yield respectively. The optimum yield of **4f** was obtained by thermal decomposition of 5-(1-azidoviny1)-2'-deoxyuridine (**V**) in dioxane (37% yield). In contrast, reaction of **U2** with $^{n}Bu_4N^{+}F^{-}$ in THF afforded 5-[2-(1-azirinyl)]-2'-deoxyuridine (**4f**) in 25% yield (**Scheme 11**).[26]



Scheme 12. Synthesis of 4g

It is known for a long time that aziridine **W**is a potentinhibitor of human placental aromatase (Scheme 11).[27] Itwas found that its inhibitory effect is based on thecoordination of the aziridine nitrogen atom with the hemeiron atom ofaromatase. The authors of a study[28]investigated the activity of its dehydroanalog, azirine **4g**,in which the lone electron pair of the nitrogen atom is evenmore sterically accessible for binding. In addition, in thepresence of a multiple bond in a three-membered ring,covalent binding in the active center of the enzymebecomes possible, which should lead to irreversibleinhibition. Azirine **4g**was obtained by the Neber reactionfrom the corresponding trimethylhydrazonium iodide. Azirine **4g**is a moderate inhibitor ofaromatase *in*

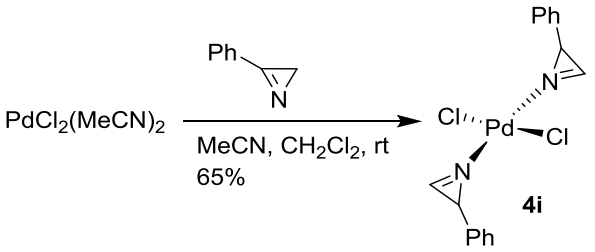
vitro (IC_{50} 5.5 μM, 2.5 M testosteronesolution was used as a substrate), less active than aziridine**W**.[27,28]



R = H, 2Cl, 3Cl, 4Cl, 2OMe, 3OMe, 2Me, 3Me, 4Me. 3Br, 4Br, $3CO_2H$, $4CO_2H$, $3NO_2$, $4NO_2$ **4h**

Scheme 13. Synthesis of 4h

Various 1-[2-(aryldiazenyl)-3-methyl-2*H*-azirin-2-yl]-ethanones**4h**was tested for antibacterial activity(**Scheme 12**).[29]They were obtained by the Neber reactionfrom the corresponding oximes.



Scheme 14. Synthesis of 4i

2*H*-azirine was synthesized from palladium acetonitrilecomplex (Scheme 9), and its cytotoxic and antimicrobialactivity was tested.[30]The cytotoxicity of complex **4i**was studied in cell linesWM115 (melanoma), HL-60 and NALM-6 (leukemia)using cisplatin and carboplatin for comparison. The IC_{50}value of complex**4i**was almost the same as that ofcarboplatin on the HL-60 cell line (4.6 and 4.3 μM,respectively) and much lower than the IC_{50} of carboplatinon WM115 cells (84.6 and 422.2 μM, respectively).However, the IC_{50} values of cisplatin in each of the threelines were lower than that of the studied complex **4i**. Theantimicrobial activity of complex **4i was** investigated bythe broth microdilution method. The minimum inhibitoryconcentration of complex **4i** for Gram-positive bacteria(*Staphylococcus aureus*, *Staphylococcus epidermidis*,*Enterococcus faecalis*) was 300 μg/ml; for Gram-negativebacteria and fungus (*Escherichia coli*, *Pseudomonasaeruginosa*, *Candida albicans*), the MIC values werehigher than 300 μg/ml.[30]

3. Conclusion

This review points to a growing interest in the development of compounds bearing azirine-moiety for biological activity in our current scenario. A future goal will be concerned with the chemical modification in the structure “design” of these new biologically active compounds by changing or insertion of one or more functional groups to heterocycle-moiety to improve “increase” their biological activity.

4. Acknowledgements

A. Majee acknowledges financial support from the CSIR-Major Research Project (Ref. No. 02(0383) / 19/EMR-II). We are thankful to the DST-FIST and UGC-SAP programmes in the department of chemistry, Visva-Bharati.

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